REMARKS

The specification is amended herein to more specifically identify the genes known in the art to be dispensable for viral replication in culture, as recited in Roizman, *Proc. Natl. Acad. Sci. (USA)* (1996), which is of record in the present application as document C89, cited in the Invention Disclosure Statement submitted February 5, 2002. This document was incorporated by reference in its entirety into the present specification (See page 11, line 4). In addition to expressly reciting the specific identities of the genes dispensable to cell culture incorporated from the Roizman (1996) reference, the specification is amended to accurately reflect that 46 HSV genes are dispensable for cell culture. Because the specification as filed incorporated by reference the Roizman article for the purpose of providing the identity of genes found dispensable for viral replication in culture, the amendment to the specification to include these genes does not introduce new matter.

Claim 1 is amended herein to clarify that administration is performed on a patient in a way such that the administered HSV infects one or more tumor cells. Support for this amendment can be found throughout the specification, *e.g.*, at least at page 4, lines 4-6, and lines 26-30. The remaining amendments to the claims correct obvious typographical errors. Accordingly, none of the claim amendments introduce new matter. Upon entry of the present amendment, claims 1-16 will remain pending and under examination.

A. Outstanding Rejections

Claims 1-4 and 15 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention.

Claims 1-5 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the written description requirement.

Claims 1-16 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly failing to comply with the enablement requirement.

Claims 1-5, 7, 9-12, and 14-16 stand rejected under 35 U.S.C. § 102(b) as assertedly anticipated by Advani (Int. Journ. Oncol. Rad. Biol. Phys 39(2 Suppl.):251), 1997) or, alternatively, Advani (Gene Therapy, 5:160-165, 1998).

Claims 1-16 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over Advani (1997) in view of Carroll et al. (1996; Ann. Surg.) or, alternatively, Advani (1998) in view of Carroll et al. (1996; Ann. Surg., 224(3):323-9, 1996).

B. Patentability Arguments

1. The rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Claim 15 depends from any of Claims 1-4 and recites the term "non-natural protein." The Examiner asserts that this term is unclear and renders the claim indefinite. Applicant respectfully disagrees.

In light of the specification, the meaning of the term "non-natural protein" is clear and precise, thereby satisfying the requirements of 35 U.S.C. § 112, second paragraph. At page 5, lines 6-10, the specification states, "[v]iruses useful in the practice of the present invention may have additional alterations in their genome that may include insertion of expressible non-natural protein encoding sequences under the control of herpes simplex virus promoters that in turn permits the sequence to be regulated as an α, β, or γ class of herpes simplex virus genes that are well known in the art." (Emphasis added.) In this context, it would be clear to one of skill in the art that "non-natural protein" is a protein encoded by an inserted sequence that is expressed from a herpes simplex virus promoter from which it is not normally, i.e., naturally, expressed. Because this definite meaning is ascertainable from the application itself and the present response unambiguously confirms that definite meaning on the record, Applicant respectfully requests withdrawal of the rejection of claims 1-4 and 15 under 35 U.S.C. § 112, second paragraph.

The instant rejection of claims 1-4 is improper for another reason. As stated in MPEP § 2121:

> There are two separate requirements set forth in this paragraph:
>
> (A) the claims must set forth the subject matter that the applicants regard as their invention; and
>
> (B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant.
>
> The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the claim is

definite--i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art.

Claims 1-4 stand rejected because they encompass all the limitations of claim 15, i.e., because of their breadth. Breadth, however, in not indefiniteness. MPEP § 2173.04. As set forth in MPEP § 2173.04, the rejection of a claim for its breadth under 35 U.S.C. § 112, second paragraph, is only appropriate when "it does not set forth that which applicants regard as their invention as evidenced by statements outside of the application as filed," i.e., when the claim does not meet the first requirement set forth above. Stated alternately, even if the line between natural and non-natural proteins were not defined clearly in the specification, Claims 1-4, each of which embraces proteins on both sides of the line, would not be indefinite. For this additional reason, the rejection of claims 1-4 under 35 U.S.C. § 112, second paragraph, is improper and should be withdrawn.

2. The rejections under 35 U.S.C. § 112, first paragraph, should be withdrawn.

a. The new matter rejections

Claims 1-5 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly directed to new matter. Specifically, claim 5 (and independent claims 1-4) stands rejected for encompassing genes that were not specifically disclosed in the specification and claim 15 (and independent claims 1-4) stands rejected for use for the phrase "HSV genome comprises an insertion of an expressible non-natural protein coding sequence." Applicant respectfully traverses the rejections.

Regarding the rejection of claim 5, the genes listed in claim 5 are specifically set forth in Roizman, *Proc. Natl. Acad. Sci (USA)* (1996), which is cited in the specification at page 5, lines 12-15, and incorporated by reference in its entirety at page 11, line 4. Applicant has amended the specification herein to expressly recite the genes set forth in the Roizman reference as dispensable for viral replication in culture. Amending the specification to expressly recite that which had been incorporated by reference does not involve the introduction of new matter. MPEP § 2163.07(b). Thus, because the subject matter of claim 5 was incorporated by reference into the original disclosure and the specification has been amended to expressly recite that specific subject matter, the rejection of claim 5 for assertedly containing new matter should be withdrawn.

Regarding the rejection of claim 15, support for the amendment to that claim can be found in the specification at, for example, page 5, lines 6-12. Thus, claim 15 does not contain new matter because it is supported by the specification as filed. Applicant respectfully requests withdrawal of the rejection of claim 15 for assertedly containing new matter.

The Examiner's rejection of claims 1-4 under 35 U.S.C. § 112, first paragraph, for assertedly containing new matter was contingent upon the rejection of claims 5 and 15 on analogous grounds. Because the rejection of claims 5 and 15 is improper, as established above, the corresponding rejection of claims 1-4 is improper.

Applicant further notes the Examiner's statement that "claims 1-4 are also rejected for encompassing the limitations for which there is no support found in the specification." (Emphasis added.) Applicant respectfully points out that claims 1-4 do not include the limitations of the dependent claims. Rather, claims 1-4 include embodiments satisfying the limitations of the dependent claims and they also include embodiments that do not satisfy each limitation of the dependent claims. OF relevance here is the fact that none of claims 1-4 recites a limitation added in a dependent claim.

Applicant additionally submits that the purpose of open-ended claiming is defeated, and settled case law is ignored, in maintaining that a claim contains new matter if it "reads on," or embraces, an embodiment not specifically disclosed in the specification. Therefore, reconsideration of the appropriateness of rejecting claims 1-4 is respectfully requested.

For the foregoing reasons, Applicant submits that the rejection of each of claims 1-5 and 15 under 35 U.S.C. § 112, first paragraph, for assertedly introducing new matter has been overcome and should be withdrawn.

b. The written description rejections

Claim 15 (along with claims 1-4) stands rejected for assertedly failing to comply with the written description requirement. Specifically, the Examiner contends that claim 15 lacks written descriptive support because the name or sequence of a "non-natural protein" is not provided in the specification. As noted above, one of ordinary skill in the art would recognize that "non-natural protein" is a protein encoded by a sequence that is expressed from a herpes simplex virus promoter from which it is not normally, i.e., naturally,

expressed. Nucleic acid sequences that are not naturally expressed from a herpes simplex virus promoter were well known to those of skill in the art at the time of filing. The recitation of an "insertion of an expressible non-natural protein encoding sequences" at page 5, line 8, of the specification would be understood by one of skill in the art to mean that the inventors were in possession of such recombinant expression units comprising an HSV promoter. That which is well known in the art need not, and preferably is not, recited in the specification. MPEP §§ 2163 and 2164.01, citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). Moreover, the particular protein encoding sequence is not an essential element of the claimed subject matter and, for this independent reason, there is no requirement to expressly recite any coding region identity in the pending claims. Applicant respectfully requests withdrawal of the rejection of claim 15 for lack of written description.

For reasons analogous to those stated above in addressing the new matter rejection, the rejection of claims 1-4 for lack of written description because each assertedly encompasses the limitations of claim 15 is improper. None of independent claims 1-4 recites a limitation added in dependent claim 15. Accordingly, the rejection of claims 1-4 and 15 under 35 U.S.C. § 112, first paragraph, for lack of written description should be withdrawn.

c. The enablement rejections

Claims 1-16 stand rejected as assertedly lacking enablement. Claims 1-4 and 15 are said to lack enabling support for an "HSV genome [that] comprises an insertion of an expressible non-natural protein coding sequence." The Examiner contends that it would take an undue amount of additional experimentation for one of skill in the art to make such an HSV. Applicant respectfully disagrees.

As stated above, nucleic acid sequences that are not naturally expressed from a herpes simplex virus promoter were well known to those of skill in the art at the time of filing. Moreover, it was routine for those of skill in the art at the time of filing to engineer HSV to place such nucleic acid sequences under control of an HSV promoter. See U.S. Patent Nos. 4,859,587 and 5,288,641, which are incorporated by reference into the present specification at page 5, lines 21-24. Thus, using the specification as a guide, it would not require undue experimentation to produce an HSV genome that comprises an insertion of an

expressible non-natural protein coding sequence for use in the method of claim 15 (or for use in the methods of claims 1-4).

A second basis for the enablement rejection was directed to each of claims 1-16. The Examiner relies on Verma et al.(Nature, 389:239-242, 1997), Chambers et al.(Proc. Natl. Acad. Sci. USA, 92:1411-1415, 1995), Crystal (Science, 270:404-410, 1995), and Advani (1998). Applicant has addressed each of these references (see Amendment of July 15, 2002) and incorporates those statements herein. The Examiner contends that the specification, while enabling for methods wherein an HSV is directly injected into the tumor, does not enable any other administration route. Despite this assertion, the Examiner acknowledges that HSV administered by a local vein inhibits the growth of metastasized tumor cells within a tissue. The Examiner dismisses this evidence, however, stating that "[t]his is different from systemic administration (encompassed by the claims) wherein the HSV is administered intramuscularly, subcutaneously, etc (such as at a distal site) and resulting in infection of the appropriate target tissue." As an example, the rejection states "systemic administration of HSV (such as by intramuscular, intravenous, or subcutaneous administration) would have no efficacy against glioblastoma, wherein the blood-brain barrier restricts entry of 120 nm HSV particles into the brain." With this statement, the Examiner implicitly acknowledges that the level of skill in the art is high. If those of skill in the art know that a particular administration route would not allow the virus to gain access to a particular tumor, they would not use such a route; rather, they would use an administration route that provides access to that tumor, *e.g.,* direct injection or injection on the appropriate side of the blood-brain barrier. The claims, however, are not limited to any specific type of tumor. Therefore, it would be inappropriate to narrow the claims to an administration route that is amenable to a particular tumor type when other administration routes, such as intramuscular, subcutaneous, or intravenous routes, are effective for other tumor types. Determining whether a particular administration route would be effective for a particular tumor is routine for those of ordinary skill in the art.

In order to expedite prosecution, however, Applicant has amended claim 1 to clarify that the administration route is such that one or more tumor cells are infected by the administered HSV, i.e., the administration route is such that the HSV particles would contact the target tumor cells. In light of this clarification, Applicant respectfully requests

withdrawal of the rejection of claims 1-16 under 35 U.S.C. 112, first paragraph, for asserted lack of enablement.

3. The rejections under 35 U.S.C. § 102(b) should be withdrawn.

Claims 1-5, 7, 9-12, and 14-16 stand rejected under 35 U.S.C. § 102(b) as assertedly anticipated by Advani (Int. Journ. Oncol. Rad. Biol. Phys 39(2 Suppl.):251), 1997) or, alternatively, Advani (Gene Therapy, 5:160-165, 1998). In support, the Examiner continues to assert that the references teach all the steps of the claimed methods using the claimed materials. Applicant respectfully disagrees. In order to expedite prosecution, however, Claim 1 is amended to recite "administering to a patient suffering from cancer. . . ." Because a patient is understood in the art as being a person (*i.e.*, human) and neither Advani reference discloses administration of HSV to a person, neither reference anticipates the present claims. Accordingly, the rejection of claims 1-5, 7, 9-12, and 14-16 under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

4. The rejections under 35 U.S.C. § 103(a) should be withdrawn.

Claims 1-16 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over either Advani (1997) or Advani (1998), each in view of Carroll et al. As discussed above, each Advani reference fails to disclose administering HSV to a patient. The Advani references do not suggest or provide motivation to administer R7020 to a person. As indicated in Advani (1998), the R7020 virus served merely as a $\gamma_1$34.5 (+) control for showing that the effect of radiation on virus replication in tumors in mice using the experimental R3616 virus was not dependent on the $\gamma_1$34.5 (-) mutation of the virus (See p. 161, last paragraph). Furthermore, nothing in Carroll et al. discloses or suggests administering to a person suffering from cancer an amount of a Herpes simplex virus (HSV) comprising a modified HSV genome wherein said modification comprises a modification of an inverted repeat region of said HSV genome such that only one $\gamma_1$34.5 gene expresses an active gene product would result in a reduction of tumor mass in CNS tumors or non-CNS tumors. Thus, the cited art relied upon by the Examiner, alone or in combination, fails to disclose or suggest an element common to each of claims 1-16, i.e., a reduction in tumor

mass in a patient. Consequently, the rejection fails to set forth a *prima facie* case of obviousness, and , for that reason, the rejection should be withdrawn.

SUMMARY

In view of the amendment and arguments provided herein, Applicant submits that each of the outstanding rejections has been overcome and the pending application is in condition for allowance.

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Respectfully submitted,

By _____

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